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MEDICINE
Review article

THE CORDOCYTE

LEON DĂNĂILĂ

National Institute of Neurology and Neurovascular Diseases, Bucharest, Romania, Clinic of Neurosurgery
Corresponding author: Leon DĂNĂILĂ, E-mail: leondanaila@acad.ro

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My research work, which led us to discover this cerebral cell (Cordocyte) has started in the 2000 years, when I have highlighted it for the first time, during a study upon clarification of some undiscovered aspects of cerebral atherosclerosis. In 2005, I have initiated the publishing our results in two atlases and at Cape Town congress in 2006. This work is based on data analysis by light and transmission electron microscopy of the surgical cases operated by me in the last 13 years. We examined cortical arteries and veins, perivascular areas with old hematic masses, vasculogenetic foci, broken large vessels, moyamoya disease, thromboses, tumors and cerebrovascular malformations, to identify and characterize different phenotypes belonging to a new interstitial cell recently described ultrastructurally in the brain and here, named cordocyte. Also, we attempted to identify and characterize precursor/stem cells for cordocytic lineage in the perivascular areas, within perivascular nerves, choroid plexus and pia mater (now considered a cordocytic-vascular tissue). This cytohistopathological study illustrates and explains some facets of cordocytes-stem cells cooperation around on the fundamental role of cordocytes in response to vascular injuries.

Key words: human brain, vessels, cordocytes, stem cells ultrastructure.

INTRODUCTION

History

My research is based on the well-known fact according to which, the brain is devoid of lymphatic tissue and lymphatic circulation.

Considering this phenomenon, I asked myself if it is possible that its functions are taken over by other elements of the central nervous system (CNS) which had not been known until today.

As a neurosurgeon, I had studied day by day, carefully, with the help of the optical microscope and of the electron microscopy, all the expansive processes and the cerebral biopsies harvested from the patients I had operated on.

In this way, beginning with 2000, I had observed the existence within the brain of a thin and elongated interstitial cell with a protective and defensive role against the various internal and external aggressions, of the most noble and most complex structure in the universe – the brain (Danaila *et al.*, 2000; Danaila *et al.*, 2002 a, b; Danaila *et al.*, 2003 a, b; Danaila *et al.*, 2004 a, b; Danaila and Pais, 2004; Danaila *et al.*, 2005).

The referred to observation, which I had initially considered to be insufficient, did not allow me to make public this new morpho-functional cerebral cytological entity.

It wasn't until the year 2005 when, following the positive rendering evident of the most important morphological (Figure 1) and physiological features, about which I did not have any doubts anymore, I had made public and I had described in two atlases the new cerebral cell I had discovered (Danaila *et al.*, 2005; Danaila and Pais, 2005).

I had postponed the official announcement of my discovery because the analized cell was very thin and thus below the resolution of the optical microscope.

The enormous amount of the material which required analyzing had made me to take on as collaborator the biologist Viorel Pais who, although

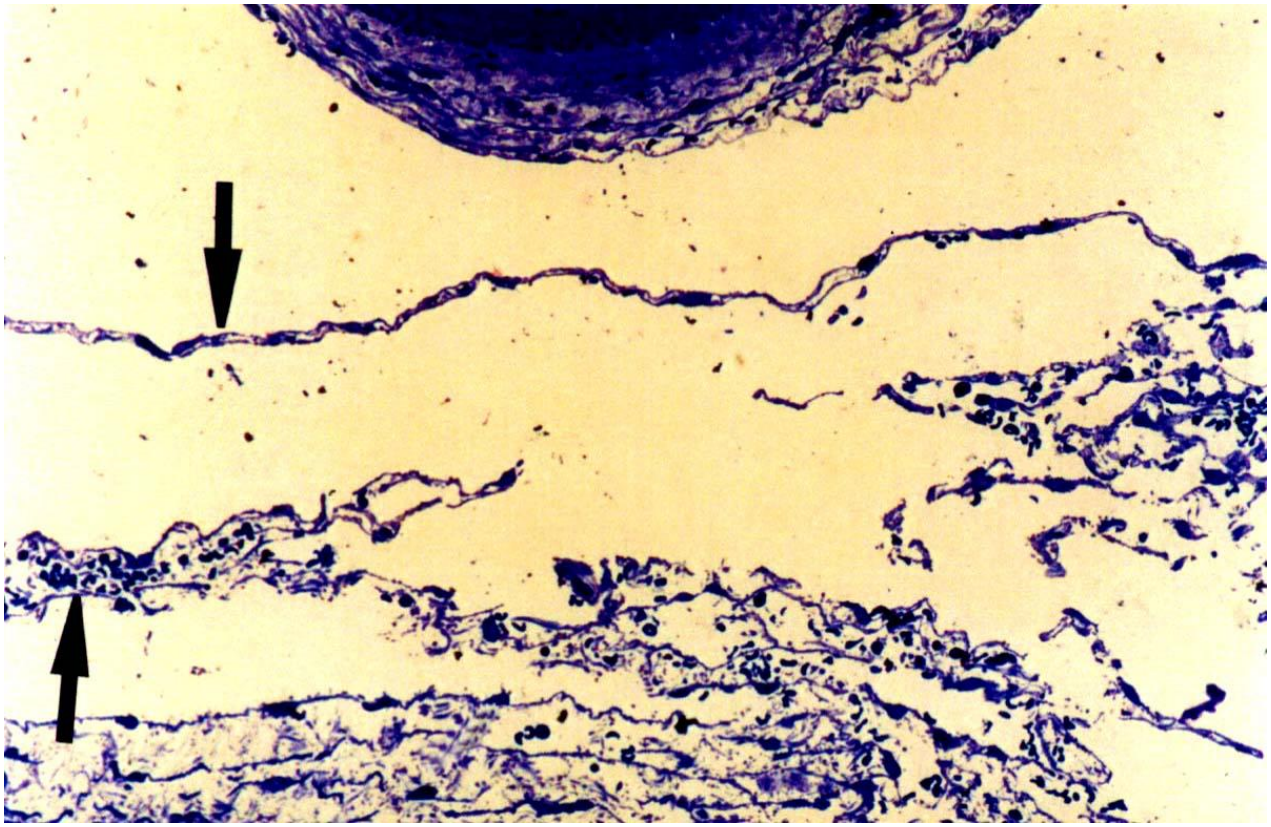

Figure 1. An arteriovenous malformation containing multiple long cordocytes arranged in parallel (arrows).

he had never worked in the Neurosurgery Department of the National Institute of Neurovascular Diseases in Bucharest, had sufficient experience in this field.

After several years, he had been pensioned off from the Ultrastructural Pathology Department of "Victor Babes" National Institute of Research Development in the Pathology Domain and Biomedical Sciences in Bucharest, and he had died on the 2nd of July 2014.

Anyhow, by having enough time at his disposal, he had been a real help for me in the selection of the figures, in their arranging into the atlases and in their drawing up, as well as in the carrying into effect of several scientific papers related to this problem, as it follows.

In 2006, we had presented the results of our research at the World Congress on Stroke in Cape Town (Danaila and Pais, 2006), and in 2008, at the 6th World Stroke Congress in Vienna (Danaila and Pais, 2008).

The first synthesis paper with reference to the morphology and the physiology of the cordocyte (already known at that time) had been published in 2011 (Danaila and Pais, 2011).

Subsequently, in 2012 and in 2013, Pais Viorel, Danaila Leon and Pais Emil had also published another two scientific papers on this topic in the "Ultrastructural Pathology" medical journal (Pais V, Danaila L and Pais E, 2012; 2013).

Emil Pais, who appears as the third and the last author of several recent scientific papers, but not of the atlases in which it is stored our entire research work relating to the cordocyte, the cellular death, the angiogenesis, etc., did not have any contribution to the early research conducted by Leon Danaila and Viorel Pais.

However, in the last two years he contributed to a paper that will be soon published in a futher issue of this Journal.

In 2014 we had published an optical and electron microscopy atlas which comprises new and innovative data with reference to the morphology and the physiology of the cordocytes in the human brain (Danaila Leon and Pais Viorel, 2014).

We had undertaken this study because this interstitial cell, which is similar, but not identical to the interstitial cell of Cajal, has a wide cerebral distribution and multiple functions which had not been reported in the literature by any other author.

We consider it to be a genuine maestro in health and diseases because of its biological potential within the cerebral parenchyma, in the areas surrounding the blood vessels, in the choroid plexuses, in the pia mater, etc.

MATERIAL AND METHODS

This paper is a summing up of our work, already published in various papers, based on the data analysis by light scanning and transmission electron microscopy of the surgical cases operated by Danaila during the last 13 years.

The ages of the patients from whom there had been harvesteed the cerebral bioptic material had been between 4 and 90 years old.

The analyzed pathological processes had included thromboses of the carotid system, cerebro-vascular malformations, aneurysms, primary hematomas, Moyamoya disease, perivascular hemorrhages, infarctions, traumatic brain injuries, metastatic brain tumors, tuberculomas, cysts, tumors (tumors of the normal choroid plexus, pineocytomas, germinomas, medulloblastomas, glioblastomas, astrocytomas, schwannomas, meningiomas, hemangiopericytomas, lymphoma craniopharyngioma, hypophyseal tumors, chordomas), abscesses, cysticercosis, hydatidosis, etc.

The normal cerebral cortex and the white matter had been harvested from the patients which had been operated for unbroken cerebral aneurysms (Danaila and Pascu, 2001; Danaila *et al.*, 2002; Danaila *et al.*, 2006; Danaila and Ştefănescu, 2007; Danaila *et al.*, 2008; 2009; 2010 a, b, c; Danaila, 2012; Danaila *et al.*, 2012 a, b, c; Danaila, 2013 a, b, c; Danaila *et al.*, 2013; Danaila and Rădoi, 2013; Danaila and Pascu, 2013).

The samples which had been studied under an optical microscope had been fixed with 2.5% buffered glutaraldehyde and post-fixed with 1% buffered osmium tetroxide, dehydrated in alcohols and embedded in resin epoxy (Epon 812). There had been cut sections with a thickness of 4-6µ using an ultramicrotome which had been then mounted on glass slides, stained with 1% toluidine blue, and examined using optical microscopy. There had also been cut with the ultramicrotome multiple ultrathin sections, with a thickness of 70 nm, which had been then treated with 2% uranyl acetate, as well as with Reynolds lead citrate solution. The specimens were then examined using the JEM 1200 EX (JEOL) transmission electron microscope.

The electron micrographs had been processed on a computer and then converted into images.

Ultrastructurally, there had been identified, characterized and compared both undifferentiated cells and well-differentiated cordocytes found in different locations, from the outer cerebral cortex to the choroid plexus, and in areas with old hematic masses, vasculogenetic foci, heterotopic neural tissue, encapsulation, broken arteries and abnormal proliferations, such as microtumors.

We had demonstrated the existence of phenotypical changes of the cells, and our findings had especially shed light on the roles of these cells which might facilitate the beneficial actions and delay the pathological processes, they being involved in the fundamental processes of the development of the central nervous system.

RESULTS

Several new histopathological features

The protective role of the pia mater cordocytes

The cordocytes, which form the pia mater together with the with blood vessels, are involved postnatally in the normal corticogenesis (which had been demonstrated in the cerebral ectocortex), in the maintenance of the appropriate pericortical microenvironment, in the vasculogenesis, vasomotion and vascular repair / remodeling, in the inhibition of the hematic invasion into the brain parenchyma as physical barriers, especially in the hypertensive human individuals, in the inhibition of the microtumoral growth and of any aberrant cellular migration towards the cerebral cortex, etc. (Figure 2).

Thus, the pia mater is composed of cordocytes. This assembly of cordocytes as the ultimate and active defender of the cerebral cortex and of the cortical vessels is a very dynamic structure, it undergoing numerous phenotypical modulation changes and accompanying various events, both in healthy individuals and during pathological processes, as a barrier within the immune surveillance.

The cordocytes and the blood-brain-barrier (BBB)

The blood-brain-barrier concept is based on the fact according to which the vital dyestuffs introduced into the blood flow do not color the brain.

Therefore, the blood-brain-barrier is the morphofunctional system which selectively regulates the access and the exit of the biological substances and of the cells, in order to control and to preserve the normal microenvironment, the morphology and the physiology of the brain.

To that effect, we had ascertained that not only the close interendothelial junctions have such a role, but the entire wall of the capillaries, of the arteries and of the veins are overprotected on the outside by well defined layers of cordocytes. (Figures 3 and 4).

The cordocytes prevent the access into the brain especially of the red blood cells, whose degradation products have a nocuous effect not only on the cerebral parenchyma, but also on the blood vessels, in which they have a spasmodic effect.

Its consequences, which can sometimes be even fatal, can be found in the patients with subarachnoid hemorrhage.

The cordocytes block the uncontrolled spreading within the brain of the red blood cells

which cross the intercellular junctional complexes which tightly connect the endothelial cells among themselves.

Our microscopic observations had been focused on the periarterial areas.

In this way, we had observed that the extravasated red blood cells are detained by the cordocytes either through adhesion or through catching. Finally, the red blood cells which had been loaded on the cordocytes are hemolyzed.

Whenever the protective cordocytic network is overwhelmed by the large quantity of red blood cells, or when these die, there are generated self-signals which concentrates numerous perivascular stem cells in the injured area (Figure 5).

In such situations, in the respective area there can be found unidentified cells, transitional forms and well defined cells.

Generally, most of our body is constantly renewed. The adult neurogenesis is the production of new functional neurons in the adult brain (Figure 6, adapted from Altman and Dass, 1965).

The cordocyte and its antitumoral role

The defensive means of the human body against cancers are equally numerous as their causes.

Therefore, during his or her lifetime, an individual can suffer and can be cured of cancer several times.

Actually, the human body can sometimes survive even the most terrible diseases.

Among the multiple defensive possibilities of the brain against the abnormally proliferating cells we can also find the cordocyte.

In such circumstances, every single cell which usually surrounds an artery can be activated, and they will position themselves in front of the abnormal cellular mass, with the nuclear long axis perpendicular to the advancing cell mass (Figure 7).

This peculiar inhibitory role of the abnormal cell proliferations is demonstrated by this cell type in the genuine tumoral cases, when large perivascular formations are closely surrounded by cordocytes, which inhibit and delay both the cell growth and their movement (Figure 8). This property to impede / delay both the cell growth and any motion is easily observable in the cases with arteriovenous malformations, where the cordocytes seem to have an efficient role in controlling the development of the neural tissue, closely surrounding all the neuroepithelial cells, and extending their filopodia towards the target cells. Moreover, overlapping cordocytes form a thick barrier between the neuroepithelial and the lymphocytic population, with the lymphocytes being separated from the neural cells (Figure 9).

In the analysis performed by Pais, Danaila and Pais (2013) there had been observed certain important aspects which we shall present as follows.

Thus, we had ascertained the interesting fact that the tumor formation is often surrounded by a thin basement membrane consisting of fibrils. The referred to thin fibrils surround each one of the tumoral cells, but not the immune cells infiltrated within the tumor mass.

The presence of the long and thin protrusions of the cordocytes around the microtumor suggests their role of antitumoral barrier.

Nevertheless, this barrier is missing here and there, while in other areas, where it is degenerated, there are found numerous peripheral thin connective fibrils.

In the zone surrounding the microtumoral mass, with areas of autophagy, the white matter is degenerated, the axons are caricatured, the oligodendrocytes are in an apoptotic phase, while the microglial cells are loaded with autophagosomes, secondary lysosomes and vascular cytoplasmic areas.

At the analysis of the transmission electron microscopy images of another tumoral node located within the white matter, in a female patient with a traumatic brain injury, we had observed an increased density of cells which appeared to be derived from the perivascular cells and the modified endothelial cells of the staghorn-shaped vessels.

These proliferated polygonal cells which surround the endothelial cells in the so-called staghorn pattern are characteristic for a hemangiopericytoma, which can metamorphose later into a true intraparenchymal tumor.

The traumatic injury could have been an etiological factor for the tumor.

In conclusion, in some tumors, the cause can be represented by the traumatic brain injury.

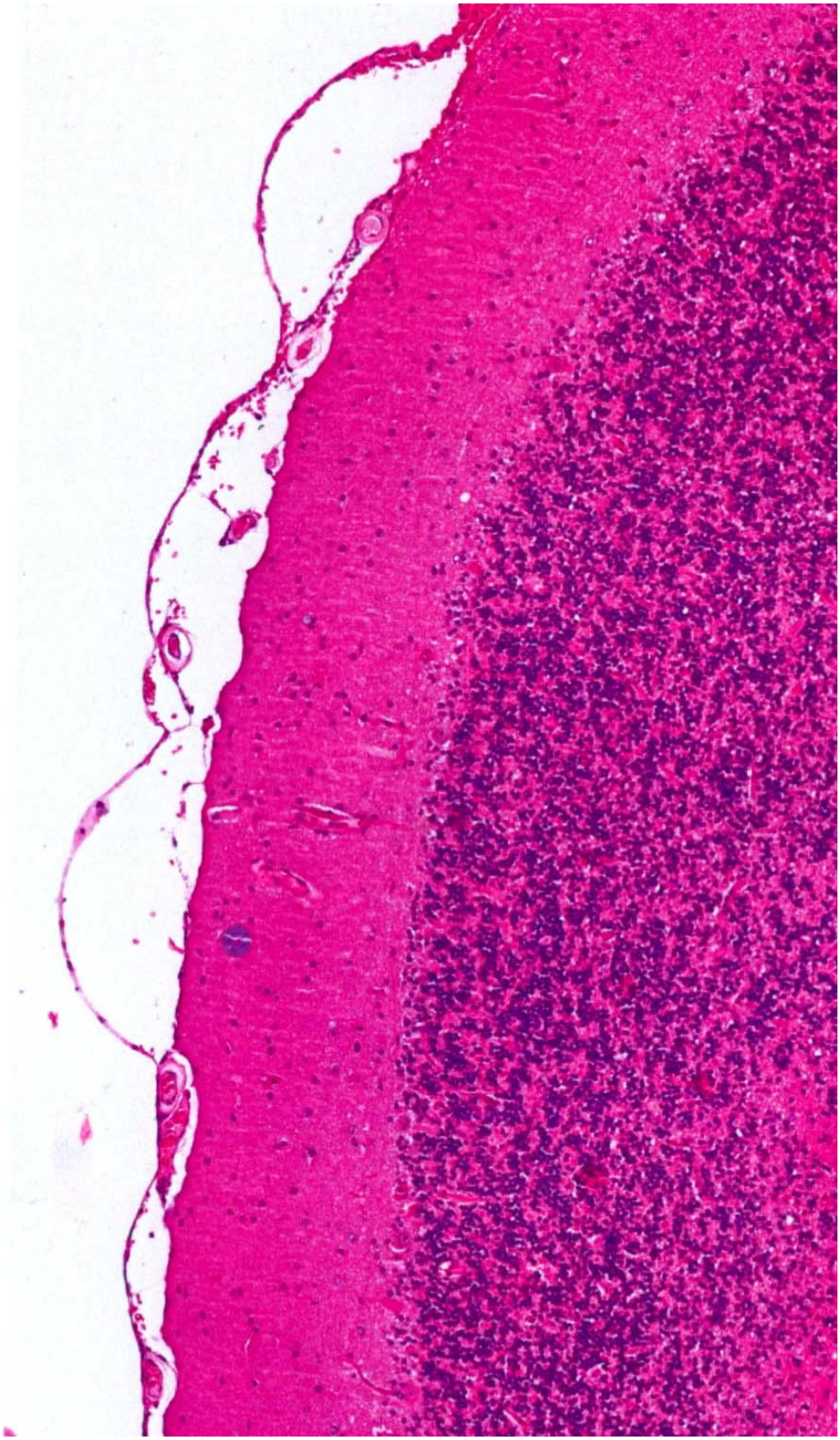

Figure 2. Pia mater, there can be seen cordocytes surrounding the pial vessels and covering the cortical surface.

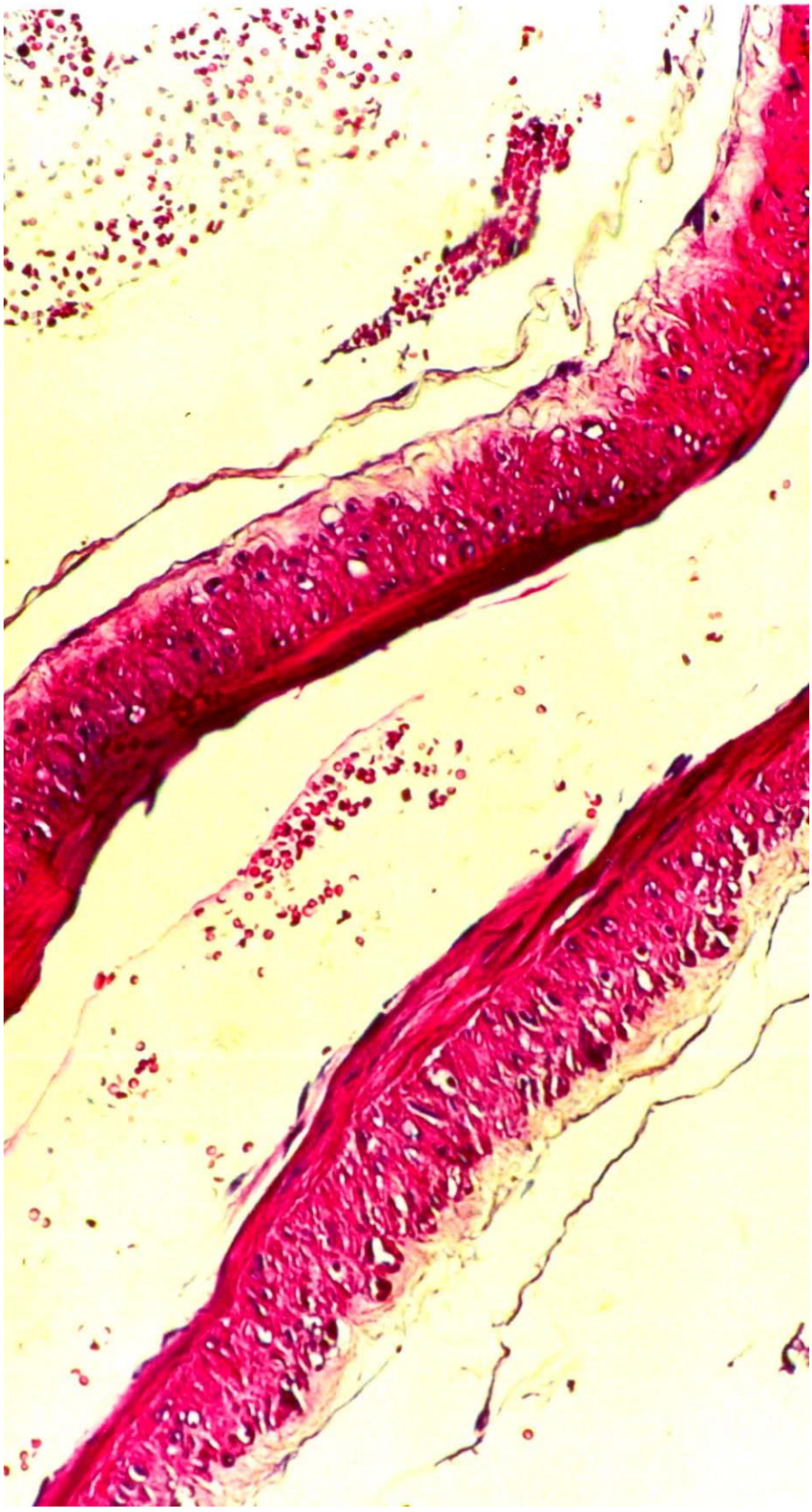

Figure 3. A portion from a cortical vein showing long cordocytes at the level of the vascular surface.

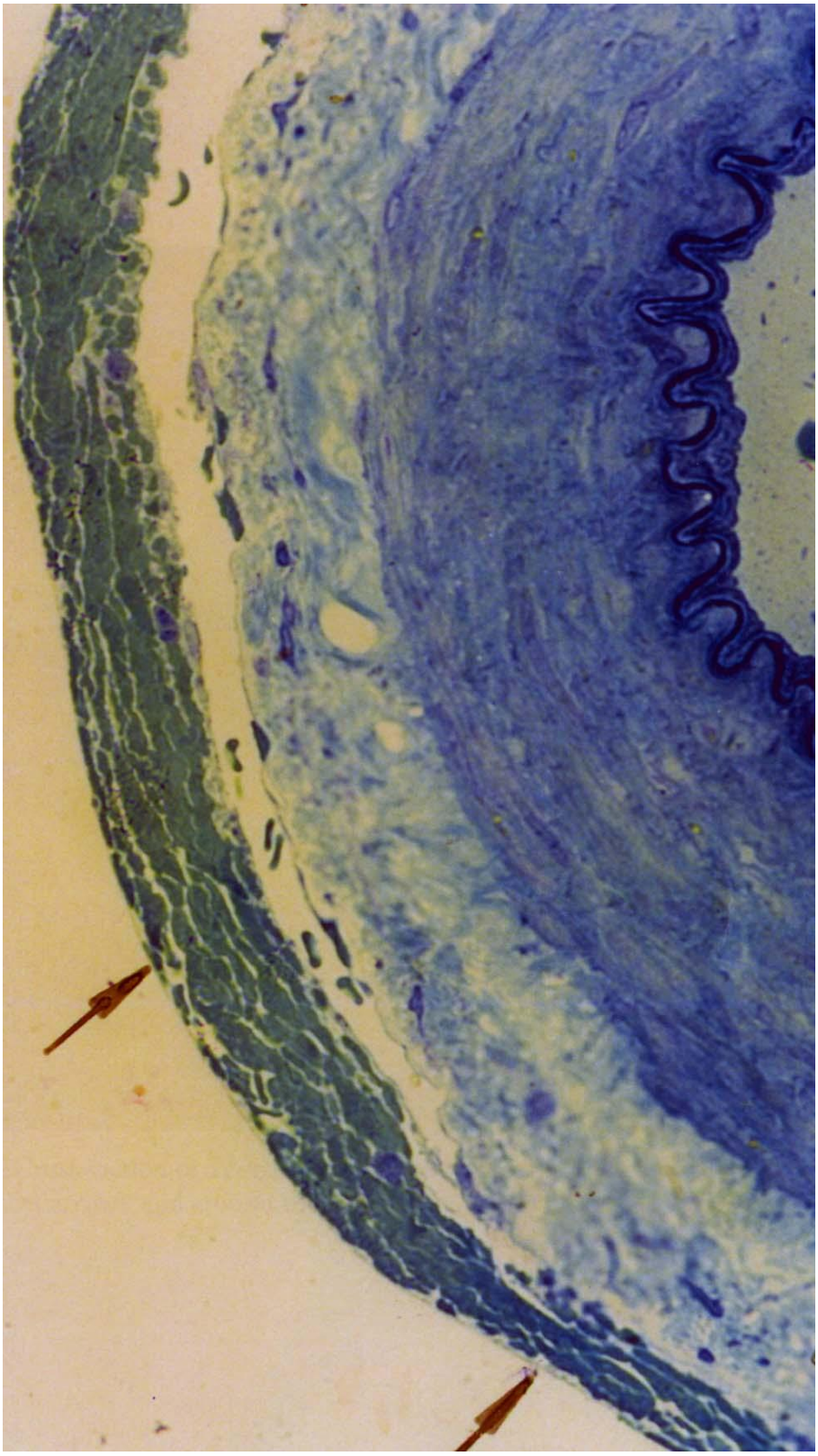

Figure 4. Multiple long cordocytic prolongations with adherent erythrocytes and a cytogenetic focus where can be seen new interstitial cells intermingled with vascular cells, in a hypertensive patient.

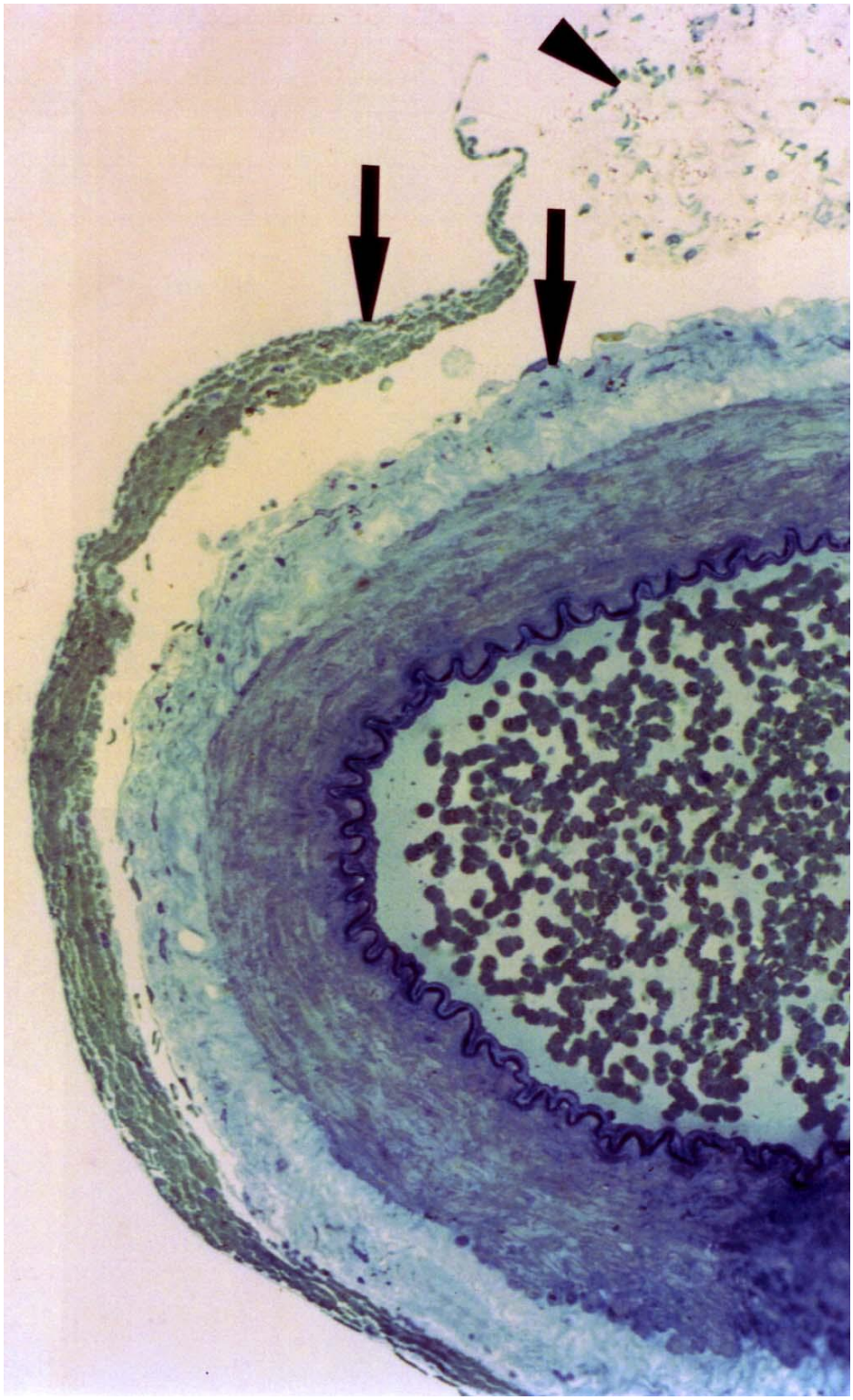

Figure 5. Periadventitial cells (arrowhead), multiple and long cell prolongations with adherent erythrocytes (right arrow), and a cytogenetic focus containing stem cells / precursors cells where can be seen new interstitial cells, in a hypertensive patient (lower arrow), (*OM* × *200*).

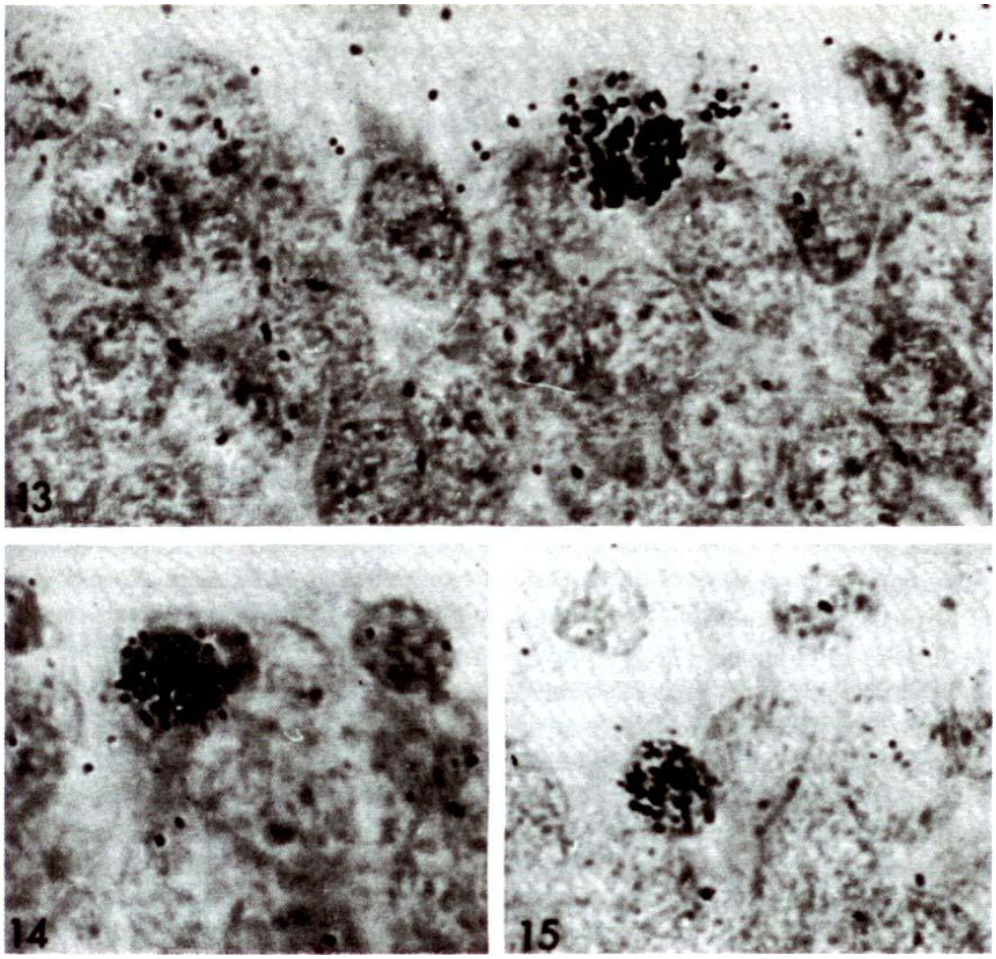

Figure 6. Altman's first image of an adult-generated neuron (adapted from Altman and Das, 1965).

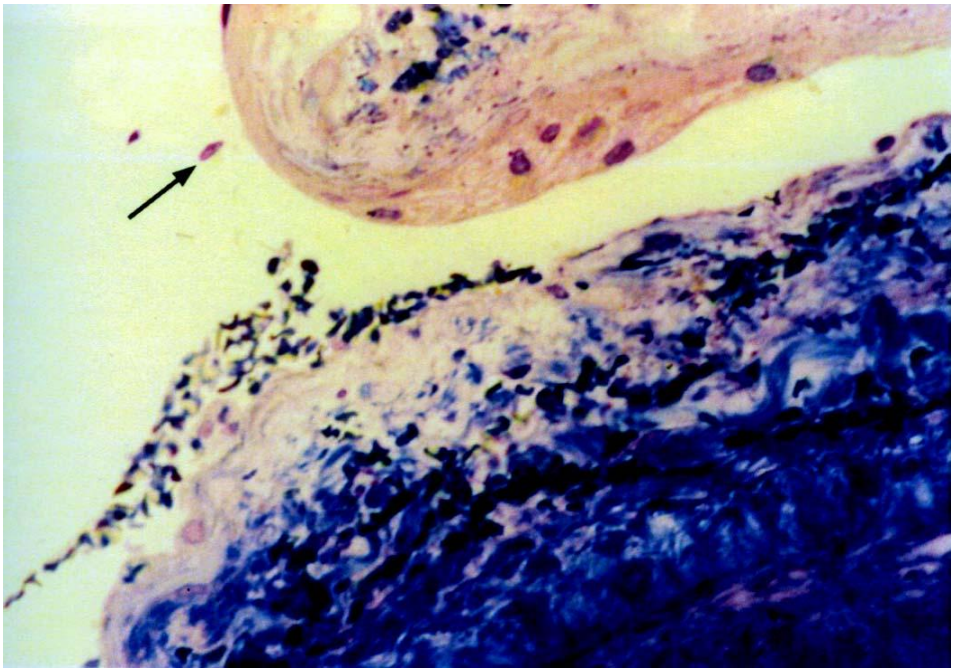

Figure 7. Abnormal cell cord around the vascular wall formed by cordocytes, which have an inhibitory role on the cell movement. This seems to be a special function of this cellular type, which comes in front of the abnormal proliferated cells with a characteristic positioning (arrow), (*OM ×400*).

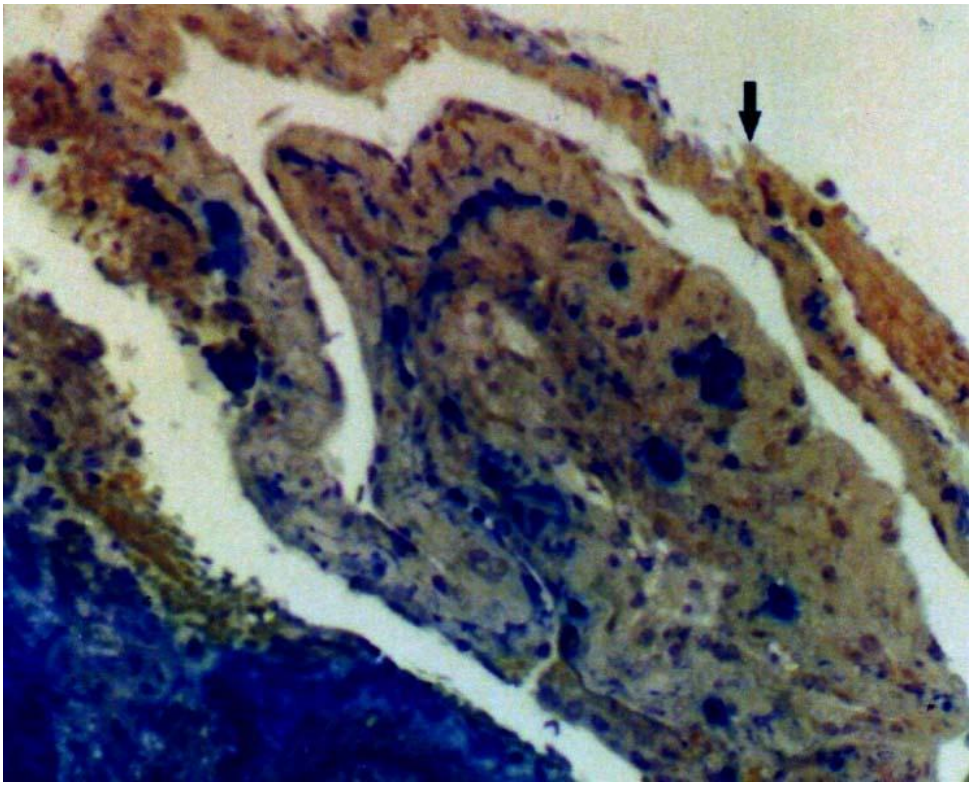

Figure 8. A solid and contorted cellular cord surrounded by cordocytes which impede the cell migration and proliferation in a case with a cerebral metastasis of a carcinoma. The arrow indicates a cordocyte firmly attached to the abnormal cells. (*OM ×200*).

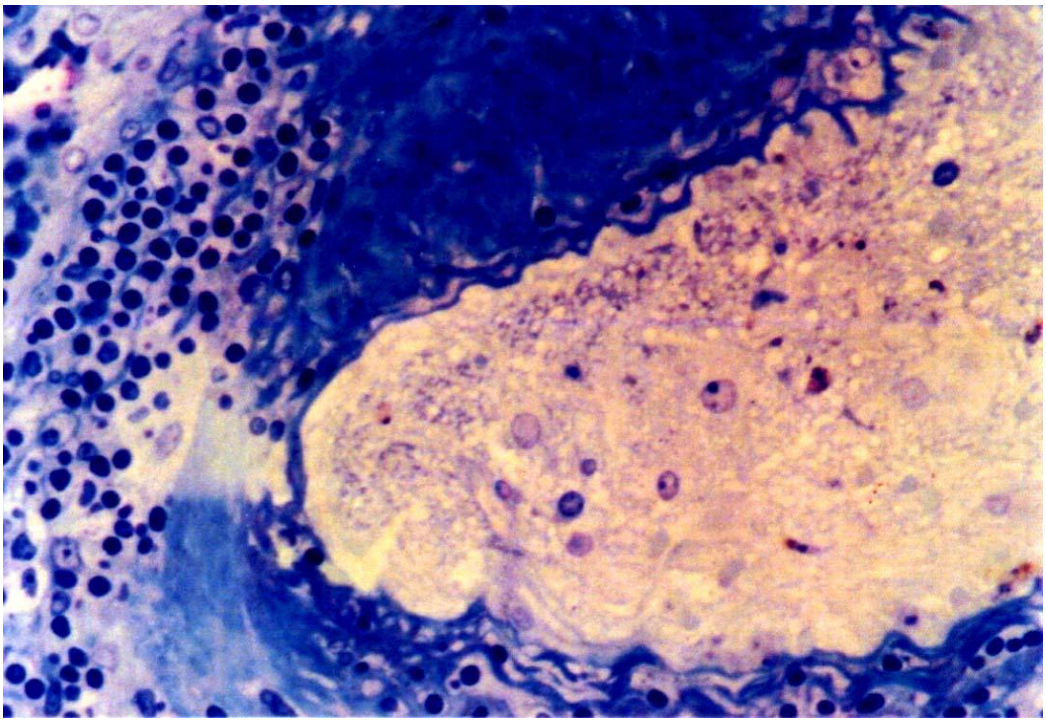

Figure 9. Neural tissue surrounded by a dense lymphocytic infiltrate, in a case with an arteriovenous malformation. All the lymphocytes seem to be separated from the neural tissue through this thick barrier formed by cordocytes. (*OM ×400*).

The repair and the regeneration of the cerebral blood vessels with the help of the stem cells, of the undifferentiated cells and of the mature or well-differentiated cordocytes

Following the study of the biopsies we had harvested from the patients with high blood pressure, from those with arteriovenous malformations (AVM) or venous malformations, as well as from those with arterial thromboses, we had ascertained the presence of the ruptures (Figure 10) and of the defects of the vascular wall (Figure 11) and the existence of the cytogenetic (vasculogenetic) foci.

In the cases of perivascular hemorrhages, the mature cordocytes surrounding the arteries and the veins have most of the times spatial and temporal relations with the undifferentiated cells and with the mesenchymal stem cells.

The cordocytes not only make a supportive interstitial network for the stem cells, but they act as regulators and modulators for the different cellular types in all the stages of the processes, they being particularly sensitive to any local damage.

In this kind of situations, some of the cordocytes remain in the proximity of the adventitial layer, while others move to the perivascular space, where they have close relationships with the isolated undifferentiated cells and with the mesenchymal stem cells from which emerge new cordocytes (cytogenetic foci) in order to clean the perivascular spaces.

Al the small cytogenetic foci contain both progenitors of the vascular cell lineage and precursor cells for the cordocytic lineage. On the other hand, all the cytogenetic foci with only several precursor / stem cells are already surrounded by one or two well-differentiated cordocyte layers, fact which suggests their important morphological roles in the early events of the vascular morphogenesis.

In this way, the well-differentiated cordocytes gradually eliminate the red blood cells from the future vasculogenetic foci.

However, in some arteriovenous malformations, multilayered cordocytes surround the proliferating precursor / stem cells, whereas the hematic mass is surrounded by a single layer of well-differentiated cells, due to the different cytokinetic mechanisms which are present in the different cell types.

Normally, the long and thin cordocyte prolongations which surround the nascent vessels suggest a controlling role of the proliferation, migration and differentiation processes.

The cordocytes gradually orchestrate all the cellular events in the vasculogenetic sequence, because they are in direct contact with the stem cells and with the different progenitors, and surround each cytogenetic focus, indifferent of its age, until the formation of the mature vessel.

All cellular divisions, migrations, and differentiations are in direct relation with the well-differentiated cordocytes which send thin prolongations toward the target cells, or surround the massive formations which contain many differentiating cells originating from the hematopoietic stem cells or from the perivascular mesenchymal stem cells.

When the well-differentiated cordocytes are absent, the precursor / stem cells are spreading in the space and not in the vascular lineages.

In the vascular segments with narrowed lumen or with occlusions, there can be observed at the vascular surface an accumulation of precursor / stem cells in association with cordocytes, or cytogenetic foci where only the cordocytes are present. Thus, these cytogenetic foci are positioned in the immediate vicinity of the disrupted vascular walls.

These are prompt reactions of the protective cells which are located around the vessels (Figure 12).

In the transmural erythrodiapedesis, sometimes the tunica adventitia is thickened and contains numerous precursor / stem cells, but not differentiated cells, cordocytic phenotypes, or vascular lineage.

The remodeling begins with the mobilization of the stem cells, followed by the proliferation and the migration toward the place of rupture of the differentiating cells of cordocytic lineage, and finally ends with the new cordocytic coverage of the vascular surface.

These spatial and temporal modification mechanisms are regulated by the cellular dynamics and morphology.

Responsible for such mechanisms are the well-differentiated cordocytes, because they come in direct contact with the stem cells through their long and thin prolongations.

Moreover, other well-differentiated cordocytes come to the damaged place, fact which suggests precise and specific signaling pathways.

Finally, when the arterial rupture is resolved through the cell cooperation, which also includes the smooth muscle cell activity within the tunica media, a new layer of cordocytes and other elements and cells covers the vascular surface (Figure 12).

However, cordocytes playing a key role are observed in some cases with arteriovenous malformations in which the tunica media is lacking in some of the vascular segments.

In this areas, well-differentiated cordocytes gather stem cells which become adherent to the cell membranes in the damaged area (Figure 12).

In the veins, there are found stem cells which are clustered together through long prolongations and short filopodia of the local cordocytes at the level of the damaged vascular wall (Figure 13).

Additionally, other mature cordocytes, reinforced by collagen fibers they produce themselves, are directed toward a crossing cell column which prevents the venous wall to collapse due to the focal degeneration.

In the patients with thromboses, there is also present a perivascular reaction of the cordocytic lineage, with polymorph nuclei, in conjunction with mature cordocytes.

Now there can be identified stem cells in symmetrical divisions in small cytogenetic foci, as well as undifferentiated or morphologically transitional cells and mature or well-differentiated cordocytes, with their characteristic ovoid nucleus and prominent and marginal nucleolus.

However, these protective cells occupy a peripheral position, at the vascular surface, surrounding the different cellular foci, in direct contact with the fibroblasts and the macrophages in the perivascular areas with new arterioles and numerous foam cells.

A thrombosed branch originating in the middle cerebral artery had showed the involvement of the cordocytes, both during the early vasculogenetic events and in the maturing vessels.

Matured and interconnected cordocytes surrounded the totally thrombosed main artery, and there could be seen both the incipient cytogenetic focus (Figure 14) and the collateral vessels in formation.

The cordocytes are always distributed to the peripheral zones of the cytogenetic / vasculogenetic foci to support the cellular actions and to protect the delicate cellular building, they producing themselves an amount of collagenic extracellular matrix as supporting connective material.

The referred to vasculogenetic process attracts from the beginning other cordocytes which position themselves at the periphery, so that in the end, at the exterior of the mature vessels there is sometimes an excess of cordocytes showing apoptosis processes (Danaila *et al.*, 2002).

At another level, a thick cell column emerges from the other adventitial layer including cordocytes and a few stem cells.

In the core of nascent vessels it is visible a segregation of the differentiating cells, some of them becoming endothelial cells, while others evolve into smooth muscle cells. The surplus cells, either endothelial or smooth muscle cells, may undergo apoptosis or autoschisis processes which are identified using the electron microscopy.

However, the continuous involvement of the cordocytes is evident in all the stages of vascular morphogenesis. Whenever a vasculogenetic focus increases in size, it is surrounded by interconnected mature cordocytes which keep inside all the cells (both undifferentiated and differentiated, i.e., stem cells, progenitors of endothelial cells, smooth muscle cells and fibroblasts) which participate in histoarchitecture of the vascular wall.

Our electron microscopy observations demonstrate a very close rapport between the perivascular cordocytes and the stem cells in the early phase of collateral vasculogenesis, when the cordocytes surround from the beginning until the end all the proliferating and differentiating cells during their maturation process towards endothelial cells, smooth muscle cells, fibroblasts and well-differentiated cordocytes.

Therefore, it is clear that the cordocyte act as a guide and as a protective cell for a cytogenetic / vasculogenetic focus, despite the reduced number of stem cells within the vascular niche (Figure 15).

The principles which control the embryonic stem cells, the proliferation versus differentiation, the paracrine mechanisms, as well as the identification of the different messenger molecules they secret themselves, remain to be comprehensively established.

According to Belting and Wittrup (2008), the novel pathways for the cell to cell communication involve nanotubes, exosomes, apoptotic bodies, and nucleic acid-binding peptides.

In conclusion, the perivascular cordocytes cooperate closely with the stem cells in the vascular repair and in de novo vessel formation through cell proliferation and cellular differentiation.

The cordocytes as anti-hematic barrier

In the cases with recent hemorrhagic foci, we had ascertained in their periphery the presence of a long and thin cordocyte with the role of anti-hematic barrier (Figure 16 a, b).

The lysed cells from the hematic mass probably generate chemoattracting agents for the referred to delimitating and neuroprotective cordocytes.

The neuroprotective action is demonstrated by the fact that there cannot be found any red blood cells beyond the cordocytes.

The cordocytes in the human brain associated with inflammation-carrying extracellular vesicles

The investigations had been performed through transmission electron microscopy (TEM), on the biopsies harvested by me (Danaila L) from the patients with intracerebral cysts, parenchymal hemangiopericytomas, arterial thromboses, Moyamoya disease, meningiomas, glioblastomas and other cerebral tumors.

In these types of cases, besides the cordocytes, we had also ascertained the presence of a number of exosome-like spherical vesicles (30–120 nm) and of microvesicles (100–1,000 nm).

The vesicles derived directly from the membrane, as well as the exosomes originated from the exocytosis of the multivesicular bodies, are dedicated to the intercellular information transport, to the biogenesis, the preservation of the normal cell functions and to the reparation of the pathological foci.

They contain messenger RNA and macro non-coding RNA, bioactive lipids, proteins, etc., which act as intercellular communication vehicles, with the potential for transferring the receptor cells.

The reciprocal changes of intercellular information take place between the stem cells, the undifferentiated cells and the adult ones, both in normal conditions and in pathological situations.

The human brain is by excellence the organ of the mutual intercellular communication between its constituent neuroepithelial elements.

The multifunctional mesenchymal cell named cordocyte which we had discovered lately is omnipresent at the level of the brain.

The information carrying microvesicles and exosomes which are generated and released by the cordocytes have an extremely important and complex role in the intercellular mediation.

We shall present further the imaging from the samples we had analyzed.

The long arrows on the microscopic images indicate the microvesicles, while the short arrows reveal the exosomes.

The close communication between the cordocyte and the smooth muscle cell within the wall of a cortical artery in a sample harvested from a case with the thrombosis of the left internal carotid artery had made the migrating cordocytic cell to get very close to the membrane of the muscle cell. The cordocyte releases continuously numerous microvesicles which are endocytosed by the smooth muscle cell.

At the periphery of the cerebral vascular walls there are always cordocytic prolongations with microvesicles in the space between them which act as homocellular information vesicles, or in the vicinity of the marginal smooth muscle cells, as a mark for the heterocellular changes (Figure 17 a).

Although the microvesicles, which are generated by the thousands, travel at a distance, they do not easily disintegrate.

They are released massively only at the level of the target cells, and not in the unpopulated spaces.

Gradually, the non-endocytated vesicles disintergrate within the collagen mass. (Figure 17 b).

The number of the microvesicles which are generated by the arachnoid cells is significantly exceeded by the number of the microvesicular bodies which release exosomes. However, a microvesicular body can contain numerous small exosomes which disappear quickly from the cellular landscape after the end of the action.

The cells also have another efficient mechanism for the conservation of their products when they reach the extracellular space. Following the proper signals, they send cytoplasmic prolongations which retain the vesicles with their adequate load in the proximity of the cell membrane.

Consequently, the cell membrane has a very important role in the vesicular circulation (Figure 17 c).

In Figure 17 d we can see how two arachnoid cells, with very dense cytoplasm and with the nucleus rich in heterochromatin, are surrounded by a large number of microvesicles and by a microvesicular body which contains exosomes. Other arachnoid cells send cytoplasmic prolongations at whose ends there are released microvesicles. Other vesicles, which had been taken over from the extracellular space through endocytosis, give rise to a bidirectional flow. Anyhow, the vesicular transfer is very intense at the level of the arachnoid mater.

However, under the influence of certain nocuous factors, the contents of the microvesicles and of the exosomes can change the phenotype of the cells in the respective microanatomical territory.

It is known that, through their contents of messenger RNA and microRNA, the exosomes and the microvesicles contribute to the tumoral development. Thus, we had ascertained that at the periphery of a tumoral nodule located within the white matter there can be found both microvesicles and exosomes (Figure 17 e).

We had also observed numerous microvesicles and exosomes as intercellular information carrying vehicles in the case of a fibrous meningioma (Figure 17 f).

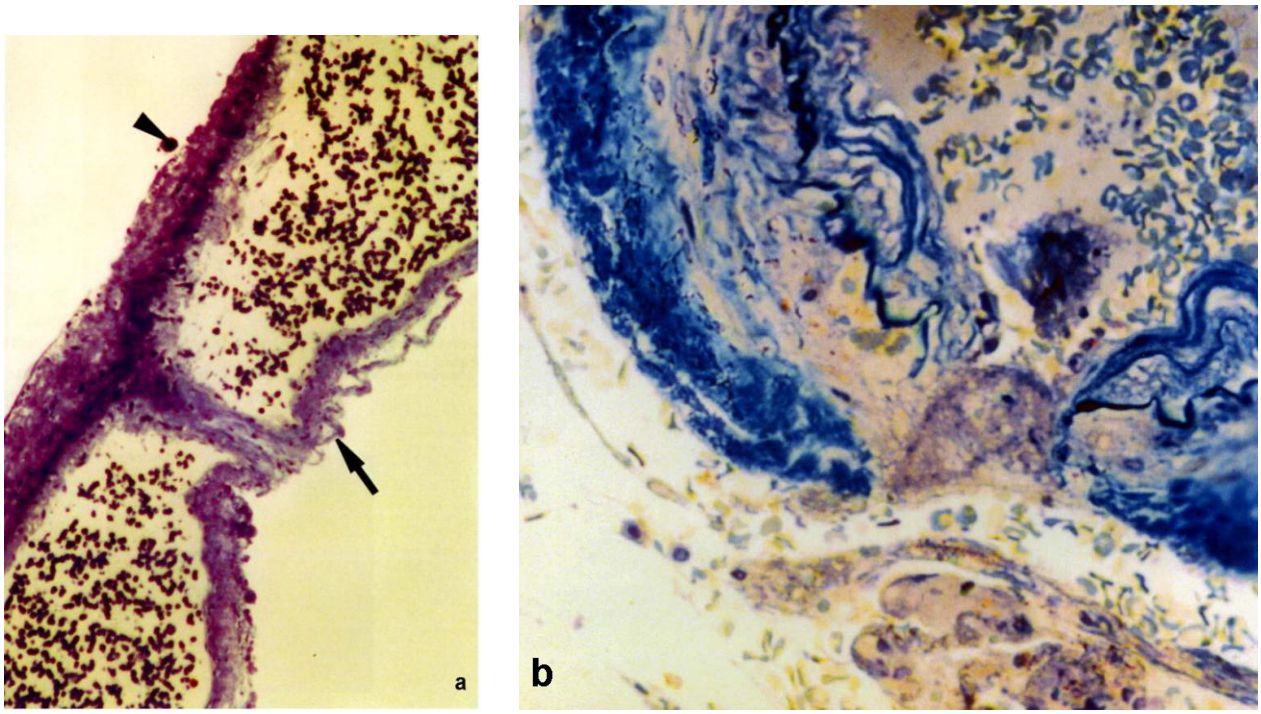

Figure 10. (a) A broken cortical vein showing an undifferentiating cell (arrowed) and long cordocytes running towards the vascular wall. (b) A broken cortical artery showing the mobilization of the precursor / stem cells and of the well-differentiated cordocytes in front of a vascular rupture, while other mature cordocytes retain the isolated red blood cells (*OM ×400*).

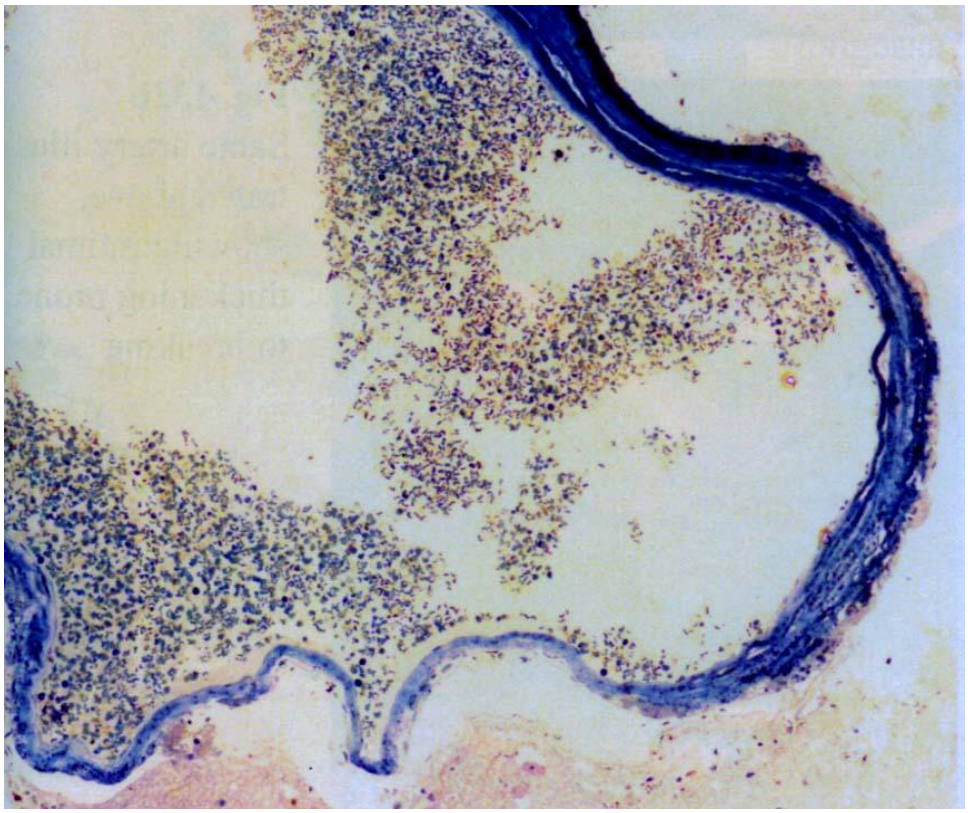

Figure 11. A vascular wall defect with a fibrous thinned wall surrounded by cordocytes and by gliotic parenchyma.

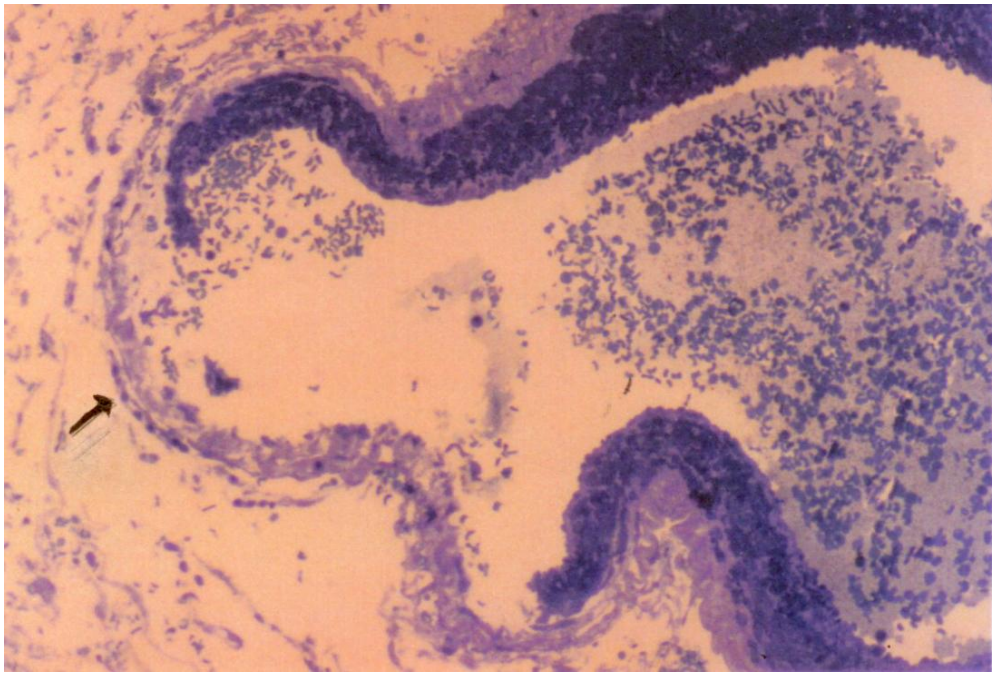

Figure 12. A poorly structured venous wall in which the tunica media is lacking. Here we can see a thick band containing collagen, stem cells, mature cordocytes, which had surrounded numerous stem cells (*OM ×200*).

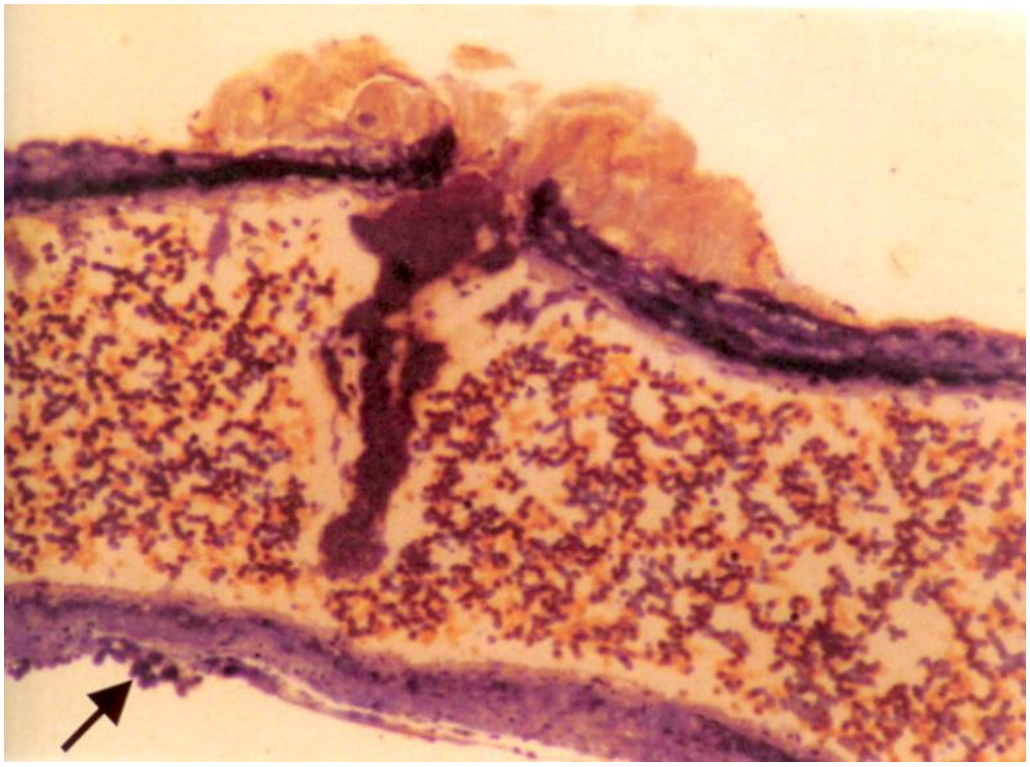

Figure 13. A broken cortical vein displaying a haemostatic platelet plug on the side with the broken and focally degenerated wall. On the opposite side, we can see the proliferation of numerous stem cells in close contact with mature cordocytes (arrow) (*OM ×200*).

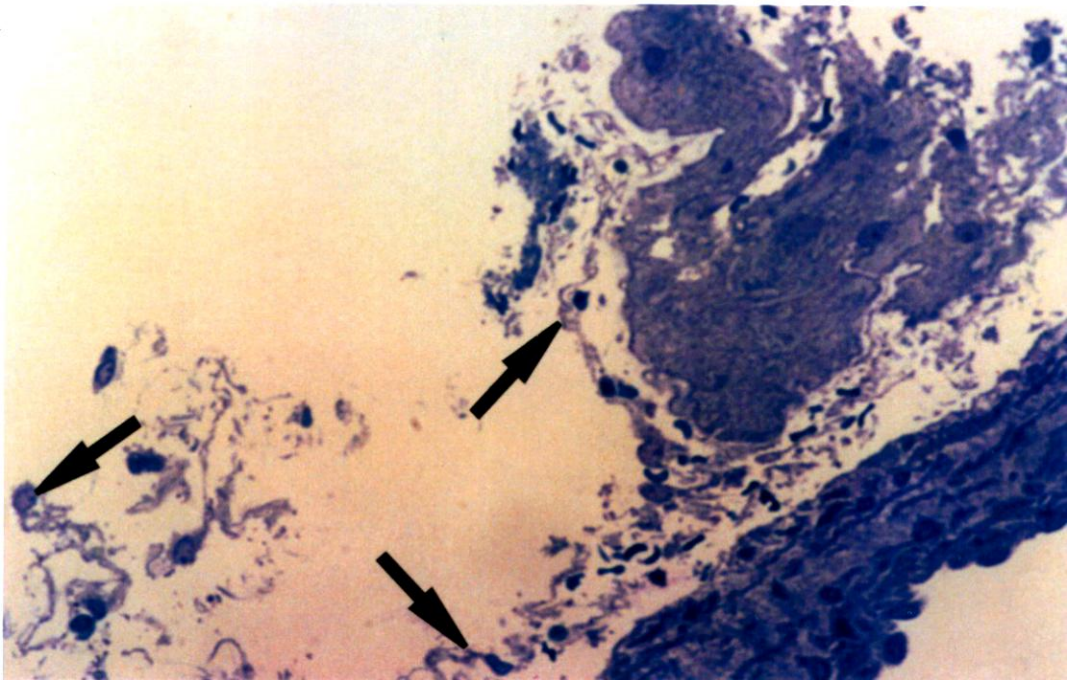

Figure 14. Numerous cordocytes surrounding a cytogenetic focus near the vascular wall (arrows).

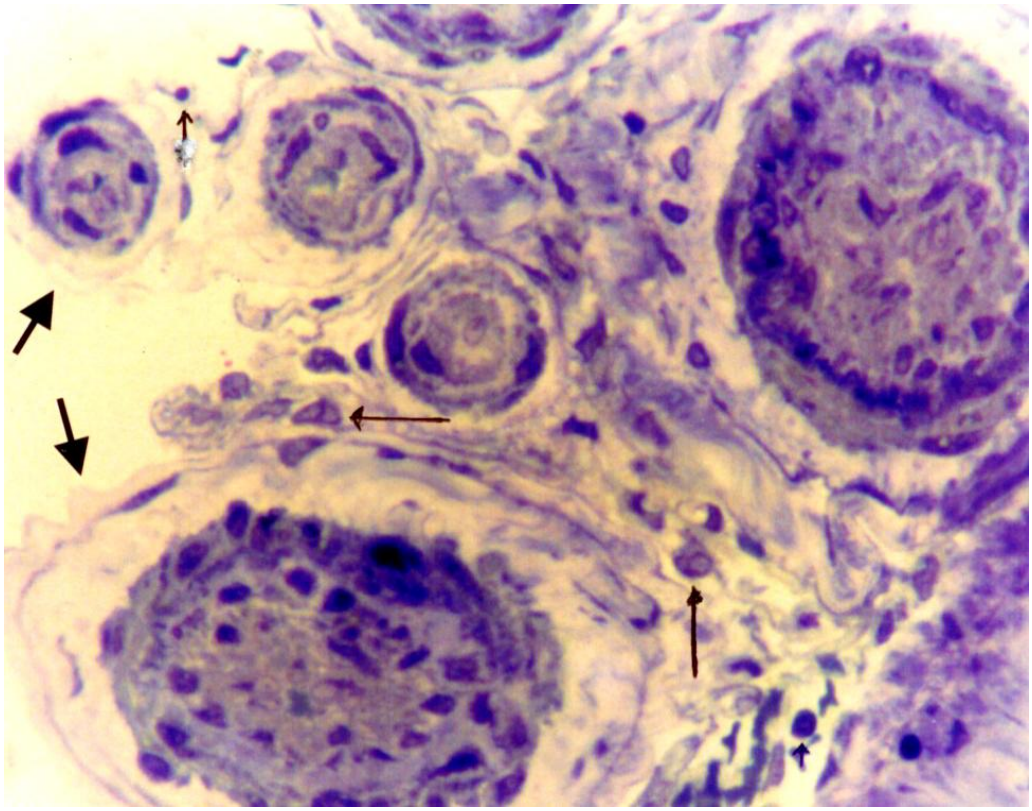

Figure 15. This image shows collateral neoformation vessels (intermediate arrows), stem cells in relation with cordocytes (short arrows), cells in divisions (very long arrows), and a double layer of mature cordocytes disposed around the new vessels (*OM ×400*).

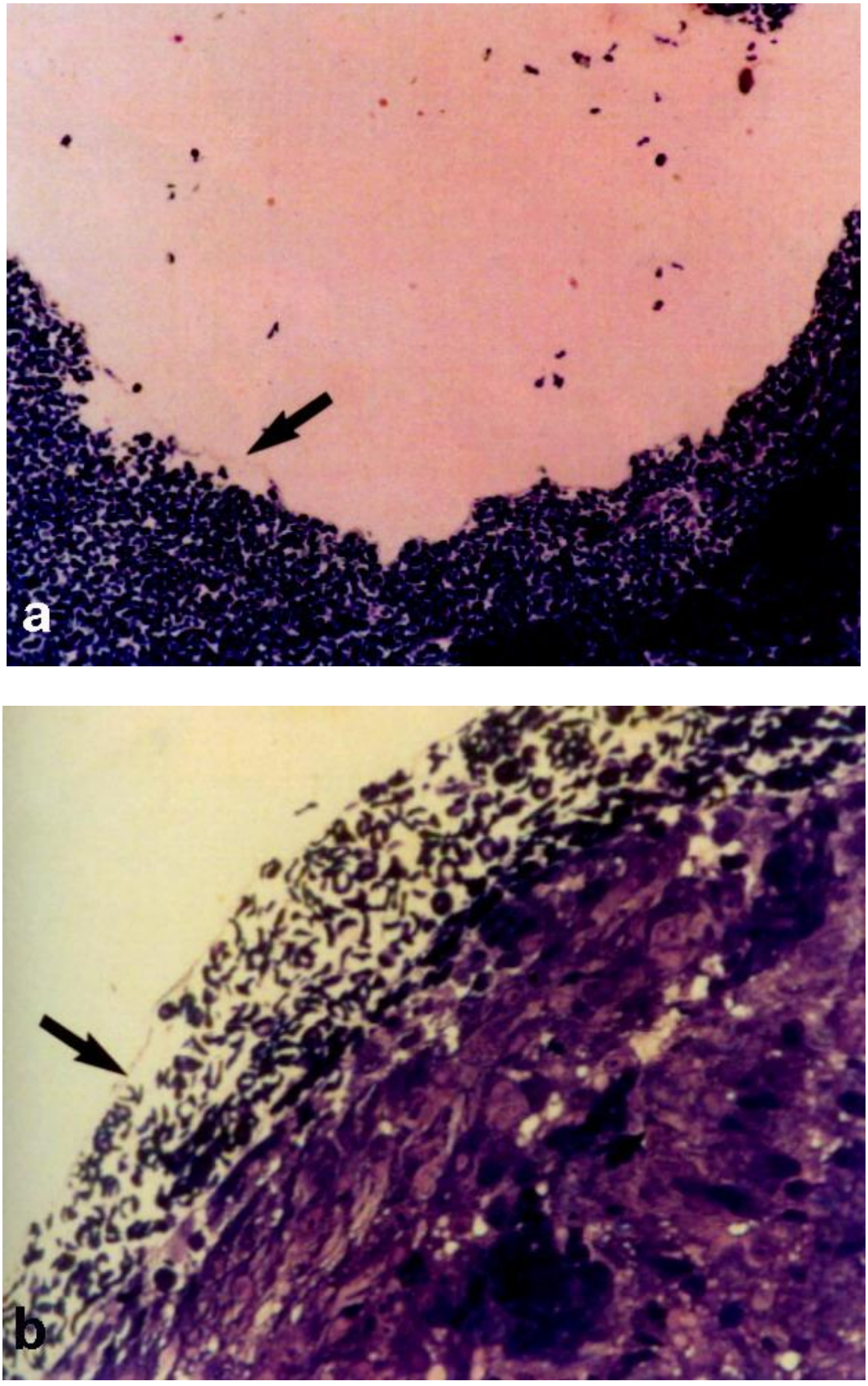

Figure 16. (a) Recent hemorrhagic focus delimitated by a thin and long cordocyte, which does not allow the red blood cells to enter into the cerebral substance. (b) In this image we can also observe the role of efficient anti-hematic barrier of the cordocyte, which is hardly visible. Beyond it there are no red blood cells.

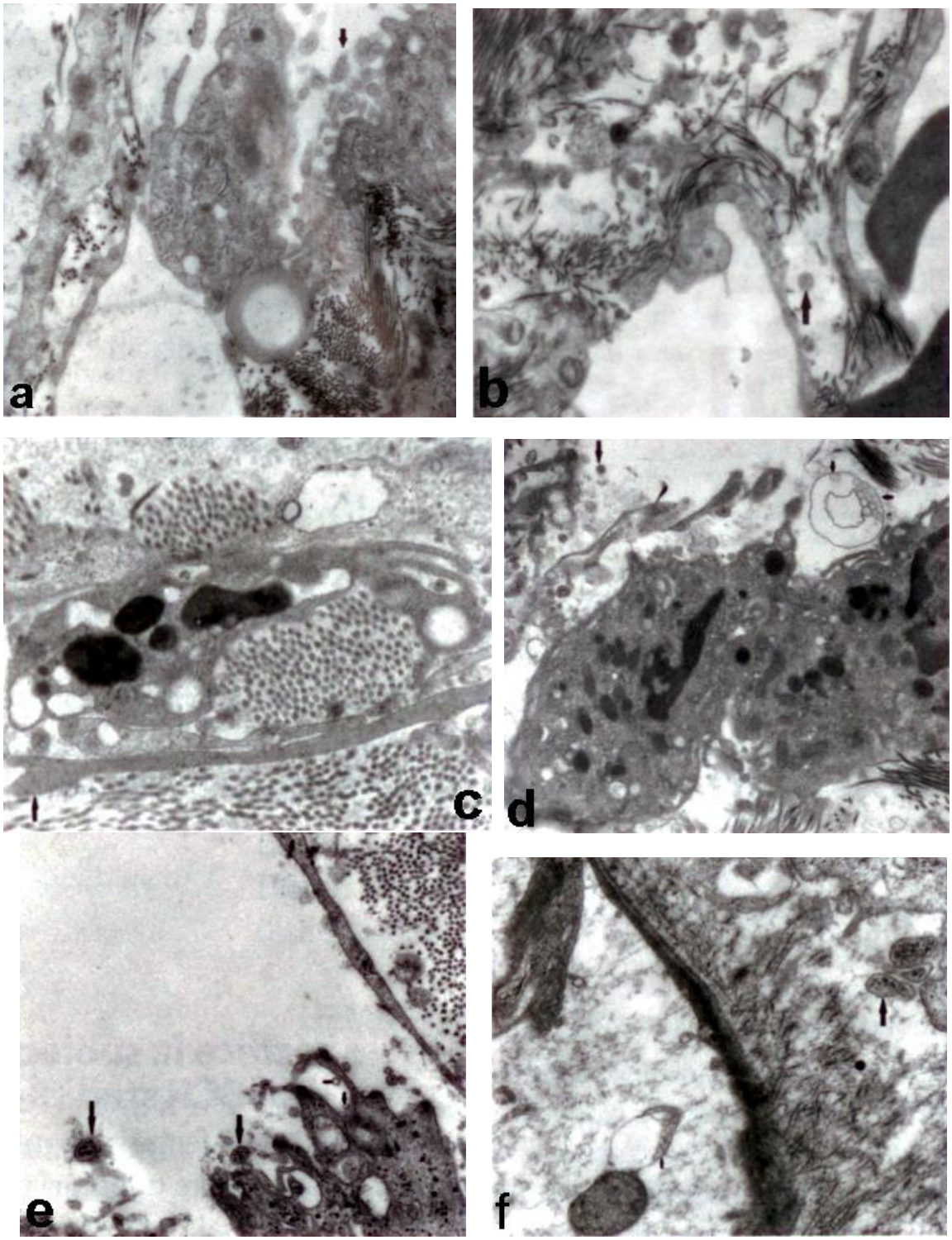

Figure 17. (a) Cordocytic prolongations with microvesicles in the space between them; (b) Non-endocytated vesicles within the collagen mass which are in course of disintegration; (c) Cytoplasmic prolongations which capture the vesicles loaded with exosomes located in the proximity of the cells. The important role of the cell membrane in the vesicular traffic; (d) Two arachnoid cells surrounded by a large number of microvesicles and a microvesicular body containing exosomes. The arachnoid cells send cytoplasmic prolongations which release microvesicles. Other vesicles are taken over from the extracellular space through endocytosis, fact which suggests the presence of the bidirectional flow; (e) The presence at the periphery of a tumoral nodule (hemangiopericytoma) of both microvesicles and exosomes; (f) We can see numerous microvesicles and exosomes surrounding the tumoral cells of an meningioma.

In this way, with the help of the electron microscopy, we had been able to identify the presence of the extracellular vesicles generated by both the damaged cells, and by the necrotic tissue.

They make up an information transport system which is indispensable for the cellular survival processes. In this context, the cordocyte is the supervising cell of the human brain.

In conclusion, the cerebral intercellular information transport is difficult to unravel. It requires a good knowledge not only of its morphology, but also of the biochemical-enzymatic equipment, of the chemoattracting agents and of each RNA molecule which is specific for each cell.

The cordocytes and their most important cerebral roles

According to the findings following our histopathological and ultrastructural studies on the human brain in a variety of clinical conditions, it appears that these cordocytes might have the following important roles:

- A competitive role in the functioning of the blood-brain barrier.
- A role in the repair and / or remodeling of the broken or defective vascular wall (both arterial and venous).
- A role in vasculogenesis, especially in the adult life, for the neoformation of collateral vessels in patients with thrombosis, with arteriovenous and venous malformations and in those with other injuries.
- A role of mechanical barrier in the periarterial areas, especially in hypertensive humans.
- A role as an isolating barrier surrounding certain infectious and hemorrhagic foci.
- An inhibitory role of the abnormal cells proliferations into the subarachnoid space, suggesting their participation in the immune surveillance, as a local defender against the microtumoral development.
- A role in the possible compartmentalization of the subarachnoid space and in the formation of channels around the cortical vessels for the drainage of the cerebrospinal fluid.
- The cordocytes in the human brain are associated with information carrying extracellular vesicles.
- I am of the opinion that pia mater is a cordocytic-vascular tissue with multiple roles in the surveillance, the protection and the support of the cerebral cortex.

CONCLUSIONS

From the cerebral biopsies I had harvested results that the cordocytes which I had discovered protect and control all the cerebral structures (the cerebral parenchyma, the blood vessels, the choroid plexus and the cerebral cortex) and that they lead a beneficial fight against all the pathological processes.

Secondly, I am of the opinion that pia mater is a cordocytic-vascular tissue with multiple roles in the protection, the surveillance, and the preservation of the pericortical microenvironment. With the help of pia mater, the cordocytes influence the vasculogenesis, the reparation and the remodeling of the arteries and of the veins in conjunction with the stem cells.

The cordocytes, together with the stem cells and with the undifferentiated cells, have an important role in the vascular repair and remodeling through the extracellular vesicles which carry bidirectional information, while at the same time they inhibit the hematic, microtumoral and infectious invasion, as well as any aberrant cellular movement towards the normal neural tissue.

The molecular and the biochemical-enzymatic mechanisms of the referred to morphological involvements remain unknown.

In the preservation of the plurifunctional phenotypes there are also involved the adult cells and the differentiation processes of the mesenchymal stem cells, as well as those of the glial transdifferentiation around the perivascular nervous tissue.

Nevertheless, these similar phenotypes with different cytogenetic origins are supported by the same molecular mechanisms.

The phenotype represents the sum of all the characters which can be observed in an individual organism. They are determined by the genes, by the dominance relationships between the alleles, and by the interactions between the genes and the environment.

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